ANTIBACTERIAL ACTIVITY OF BEROLINE

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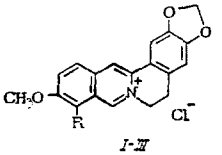
UDC 615.281:547.94].07

Synthetic studies on the alkaloid berberine are of considerable interest because of its different pharmacological, chemotherapeutic, cholagogic, antitumor, antimicrobial, and other properties [4].



I-III

Berberine chloride (I, R = OCH_3) when heated eliminates CH_3Cl and is converted to the phenolbetaine – berberubine (II, R = O^-). The latter can react with CH_3I to give berberine iodide [3]. Using the principle of this reaction, starting from berberubine the authors obtained a new salt – 9-berberoline chloride (beroline, III, R = OH).

The UV absorption spectrum of a 0.01% methanol solution of beroline is characterized by maxima at 236 nm (log ε 4.27), 260 nm (log ε 4.24), 344 nm (log ε 4.20), 410 nm (log ε 3.58). IR spectrum, ν, cm^{-1}: 1637, 1601, 1575, 1484, 2951, 2860 (OCH_3), 1605, 1640 (C=C), 1288, 1265, 1043 (C–O–C), 1275 (phenolic hydroxyl, 2900, 3040 (CH_2, CH_3). In the mass spectrum, apart from the molecular ion peak M^+ 358, peaks are recorded with m/e 353, 338, 324, 294, 158. PMR spectrum: 3.8 (3H, OCH_3), 5.8 (2H, O–CH_2), 3.07, 4.65 [2H, CH_2(5), 2H, CH_2(6)], 6.6-9.4 ppm (aromatic protons). The phenolic hydroxyl undergoes exchange with deuterium.

EXPERIMENTAL (CHEMISTRY)

UV spectra were recorded on a Hitachi EPS-3T spectrophotometer, IR spectra were recorded (KBr) on a UR-10 instrument, and NMR spectra were recorded on a Tesla BS 487 C instrument at 80 MHz in CD_3OD (internal standard HMDS; chemical shift in ppm). Mass spectra were recorded on an MX-1303 instrument fitted with a system of direct introduction into the ion source. The compound was chromatographed on a thin layer of alumina (activity II-III, neutral on the Brockman scale) with development of the spot using Dragendorff's reagent.

Beroline (9-Berberoline Chloride, III). Compound II (2 g) was dissolved in 100 ml of absolute chloroform and the solution was saturated at room temperature with purified hydrogen chloride. A brick-yellow, finely crystalline precipitate was formed, which was completely separated out by absolute ethyl ether. The product was repeatedly recrystallized from an alcohol solution of ethyl ether. Yield 2.1 g (94.1%), mp 245°C (with decomp.), R_f 0.56 (systems: n-butanol–acetic acid–water, 4:1:5; chloroform–ethanol, 2:1). Found, %: C 63.32, H 4.69, N 3.86, Cl 9.81. $C_{19}H_{17}O_4NCl$. Calculated, %: C 63.0, H 4.74, N 3.9, Cl 9.9. Beroline is readily soluble in ethanol and methanol, chloroform, acetone, and water; it is insoluble in ether.

TABLE 1. Antibacterial Activity of Beroline

Compound	Maximum suppressive concentration, μg/liter					LD_{50}, mg/kg
	Staphylococci	Protei	Streptococci	E. coli	Shigella	
Berberine	1,5	12,5	12,5	12,5	3,1	30
Beroline	0,75	1,5	1,5	0,75	0,75	350

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 11, pp. 1348-1349, November, 1988. Original article submitted August 18, 1987.

 0091-150X/88/2211-0856$12.50 © 1989 Plenum Publishing Corporation

EXPERIMENTAL (PHARMACOLOGY)

Antibacterial activity was studied by means of twofold batch cultures in a liquid culture medium corresponding to the microorganisms followed by inoculation of a pathogenic culture [2]. Lines of Staphyloccocus, Streptococcus, E. coli, Proteus, and Shigella were used in the study.

The experimental data obtained from the studies on antimicrobial activity indicated that the inhibitory activity of beroline was considerably strengthened by replacement of the methoxy group by hydroxyl at the 9-position of the isoquinoline ring (see Table 1).

The acute toxicity of the compounds was studied in white mice of weight 18-23 g. The LD_{50} values were calculated by the method of Kerber [1]. Agents were introduced in increasing doses.

It was shown from the experiments carried out that the inhibitory properties of the modified alkaloid were more pronounced and the acute toxicity had decreased substantially.

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SYNTHESIS AND RADIOPROTECTIVE ACTIVITY OF 2-PHENYLETHYLAMINE DERIVATIVES

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UDC 615.849.1.015.25:547.568].012.1

It has previously been shown [1, 2] that the radioprotective activity of 1-(m-hydroxyphenyl)-2-aminoethanol (I) is very dependent on the substituent at the nitrogen atom; it was found that compound I, and also its N-methyl (II) and N-ethyl (III) derivatives are very effective.

It was of interest to evaluate the role of the substituent at the β-carbon atom of the hydrocarbon chain in compounds of this type in the manifestation of the radioprotective effect, and hence to clarify whether the presence of a hydroxyl group in this position was necessary for obtaining this effect. For this purpose we synthesized a series of derivatives of I – II and III, and also the unsubstituted benzene ring analog, 1-phenyl-2-aminoethanol (IV).

We chose the corresponding chlorides (V-VII) as the starting materials, since it has been reported [6] that the hydroxyl group at the β-position of amine (IV) is readily replaced by chlorine by the action of $SOCl_2$. It has been also reported [8] that during the substitution of the OH group by halogen in compounds with phenolic hydroxyls, the latter have to be protected by an acyl group. However, the hydrochloride of (III), similarly as that of IV, reacts readily with $SOCl_2$ with the formation of chloride VII. In the case of the methyl analog milder conditions are required.

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 11, pp. 1349-1355, November, 1988. Original article submitted August 14, 1987.

0091-150X/88/2211-0857$12.50

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